Background Novel immune cell-based treatment options are evolving for patients with acute myeloid leukemia (AML). The identification of a suitable target antigen with a restricted expression profile is still a major challenge and a prerequisite for success. CD70, which is transiently expressed in activated T-, B-, and NK cells, has been reported to be aberrantly expressed on AML and leukemic stem cells. While the mechanism driving its expression in AML is not defined, its restricted profile in normal tissues makes it an ideal target for immunotherapeutic strategies.

Methods We evaluated CD70 expression by flow cytometry on primary AML cells from initial diagnosis (ID, n = 123) and relapse (RL, n = 14). NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) assays utilizing a sugar-engineered anti CD70 antibody with a nonfucosylated Fc backbone (SEA-CD70) were performed against AML cell lines with varying CD70 expression levels and primary AML cells (n=6). Modulation of CD70 and CD33 expression and susceptibility to ADCC were analyzed in a pro-inflammatory environment achieved by either supplementation of tumor necrosis factor alpha (TNF-alpha) and interferon gamma (IFN-gamma) or by the addition of conditioned media (CM) from a CD33xCD3 bispecific-based model system for T-cell activation.

Results The percentage of CD45dimSSClow AML cells expressing CD70 ranged between 0.2 – 89.6% (mean = 15.2%) at ID and 0.3 – 90.3% (mean = 25.4%) at time of RL. SEA-CD70-mediated ADCC against AML cell lines was dependent on antigen expression level and antibody concentration (n= 4, CD70bright93.1%, CD70 dim47.6%). Specific lysis of primary AML cells ranged from 9.5 to 33.2% (mean = 20.1%). Interestingly, pre-conditioning with TNF-alpha/IFN-gamma or CM from CD33xCD3-activated T cells resulted in a significant increase of CD70, but not CD33 expression on AML cell lines (fold change in MFI ratio: 2.7, n=5). However, CM or TNF-alpha/IFN-gamma treatment also reduces NK cell ADCC activity in a target-independent manner resulting in a reduction of CD70-mediated cell lysis from 74.8% to 36.5% (n=4), and CD33-mediated cell lysis from 81.8% to 30.5% (n=4).

Conclusions Our findings validate CD70 as a target antigen in the setting of AML and show that pro-inflammatory stimuli lead to an upregulation of CD70 expression on AML cells. However, these pro-inflammatory stimuli inhibit NK-mediated ADCC activity. This data warrant future studies to understand how modulation of the TME may be utilized as a strategy to enhance target expression without negatively impacting effector cell functions.

REFERENCES

Ethics Approval Peripheral blood or bone marrow samples were collected from healthy donors and patients with acute myeloid leukemia at initial diagnosis, relapse, or complete remission after written informed consent was received in accordance with the Declaration of Helsinki and approval was granted by the Institutional Review Board of the Ludwig-Maximilian-Universität (Munich, Germany, reference number: 216-08).